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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/012,904	01/23/98	MEADE H	TCI-028DV

HM12/0815

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EXAMINER	
QIAN,C	
ART UNIT	**PAPER NUMBER**
1633	15

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No. 09/012,904	Applicant(s) MEADE ET AL.	
	Examiner Celine Qian	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

Claims 19, 21-23, and 25-30 are pending.

The request filed on 6/8/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/012904 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 19, 21-23, and 25-30 are rejected for reasons stated in the office action mailed 5/8/00 because applicants have not responded to the rejections set forth in said office action. For applicants' convenience, the office action mailed 5/8/00 is reproduced below.

Specification

The disclosure remains objected to because of the following informalities: Applicants are required to update the priority data to indicate that Application Serial No. 08/170, 579, is now U.S. Patent No. 5,827,690.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims19, 21,22,25,27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments with respect to claims 19, 21, 22, 25, 27-30 has been considered but are moot in view of the new ground(s) of rejection.

Claim 19 is rendered vague and indefinite by the phrase "unique restriction site" as it is unclear to what the unique restriction site is related, e.g., the promoter, the immunoglobin protein-coding sequence, or the 3' non-coding sequence. In addition, each restriction site is in itself unique. Thus the metes and bounds of the phrase are unclear.

Claims 19 and 28 are rendered vague and indefinite by the term "immunoglobin" as there is no previous recitation of this term in the claim. Thus, the term lacks antecedent basis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Applicant's arguments with respect to claims 19, 21-23, and 25-30 have been considered but are moot in view of the new ground(s) of rejection.

Claims19, 22, 23, and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90, newly applied).

Meade et al. Disclose a DNA construct for production of recombinant proteins comprising a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, operatively linked to a DNA sequence coding for a desired recombinant protein through a DNA sequence coding for a signal peptide that permits the secretion and maturation of the desired recombinant protein in the mammary tissue. The milk-specific protein promoter or promoter sequence specifically activated in mammary tissue can be selected from the casein promoters, or β-lactoglobulin promoter (see, e.g., column 3, lines 1-15). The DNA sequence coding for a desired recombinant protein can include sequences encoding immunoglobulins (see, e.g., column 3, lines 30-40); thus, it would have been obvious to provide DNA sequences encoding the heavy and/or light chains of the immunoglobulins to generate recombinant proteins in mammary tissue.

Meade et al. Do not disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobin coding sequence is inserted into the restriction site. However, DeBoer et al. disclose a construct comprising the αSi casein promoter and 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and 3' non-coding sequence (see, e.g., Figures 5-7).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the vector of Meade et al. by providing a unique restriction site, such as XhoI between the promoter and 3' non-coding sequence as disclosed by DeBoer et al. for

the purpose of providing a vector which is amenable to accommodating the insertion of cDNAs encoding protein of interest. One of ordinary skill in the art would have been motivated to provide such modified vectors to obviate any undesirable cleavage of the cDNA inserts which intrinsically contain common restriction endonuclease recognition sites. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA into the vector without undue experimentation barring evidence to the contrary.

Claims 19, 21-23 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316, 1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076, 5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Bischoff et al. (FEBS Letters, 305:265-268, 1992), Buhler et al. (Bio/Technology, 9: 835-838, 1991), Gordon et al. (Bio/Technology, 5: 1183-1187, 1987), Ebert et al. (Bio/Technology, 8: 140-143, 1990), and Stinnakre et al. (FEBS Letters, 284:19-22, 1991).

The claimed DNA construct comprising a coding sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence, and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site, is obvious in view of the disclosures of Meade et al. and DeBoer et al. as discussed in the above rejection.

The references of Meade et al. and DeBoer et al. do not disclose that the promoter can be selected from whey acid protein promoter or the lactalbumin promoter. However, Bischoff et al. disclose a construct containing a sequence encoding a human α1-antitrypsin variant operatively linked to 17.6 kb of the rabbit whey acid protein promoter, which results in expression and secretion of the a1-antitrypsin variant into milk of a transgenic mouse (see, e.g., page 265, under "DNA construct", page 266, right column, first two paragraphs, and Table 1). Similarly, Gordon et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator (t-PA) operatively linked to the promoter an upstream regulatory sequences from the murine whey acid protein gene, which results in expression and secretion of t-PA into milk of a transgenic mouse (se, e.g., pages 1183-1185, under the sections entitled "Construction of t-PA expression vector", and "Expression of biologically active t-PA in milk). In addition, Ebert et al. disclose a DNA construct containing a sequence encoding human tissue plasminogen activator operatively linked to the mouse whey acid protein promoter which results in expression of the protein into goat milk (see, e.g., page 835, right column, under "Generation of transgenic goats", page 836, Figure 1, and page 837, left column, under the section entitled "Expression of tPA in milk"). Moreover, Stinnakre et al. disclose a DNA construct comprising a sequence encoding ovine trophoblast interferon operatively linked to the promoter of the ovine α-lactalbumin gene, wherein the construct is capable of being expressed in the mammary gland of mice and secreted into milk (see, e.g., page 19, right column, under the section entitled "Establishment of the hybrid construct", page 20, under the section "Expression of the transgene", and Figure 1, and page 21, Table 1). From the teachings of Bischoff et al., Gordon et al., Ebert et al., and Stinnakre et al., one of ordinary skill in the art would have had a high expectation of successfully

producing a protein by the mammary gland which is secreted into the milk of a mammal using a DNA construct which contains a whey acid protein promoter or a lactalbumin promoter, which is known in the art to direct the expression of foreign protein in the mammary gland.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA construct of Meade et al. by providing a unique restriction site, such as XhoI between the promoter and 3' non-coding sequence as disclosed by DeBoer et al. for the purpose of providing a DNA construct which is amenable to accommodating the insertion of cDNAs encoding proteins of interest. Moreover, it would have been obvious to further modify the DNA construct by substituting the casein promoters or β-lactoglobulin promoter, with promoter sequences obtained from the whey acid protein gene or α-lactalbumin gene in view of the teachings of Bischoff et al., Gordon et al., Ebert et al., and Stinnakre et al. that these promoters direct expression of foreign proteins in mammary epithelial cells. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as tissue specific expression, and ease of insertion of various cDNAs of interest into the vector, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA without undue experimentation barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Claims 19, 22, 23, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade et al. (U.S. Patent No. 4,873,316,1989), taken with DeBoer et al. (U.S. Patent No. 5,633,076,5/27/97, effective filing date of 11/27/90) as applied to claims 19, 22, 23, and 25-28 above, and further in view of Boss et al. (U.S. Patent No. 4,816,397, 3/28/89), Bruggemann et al. (WO 90/04036, 1990), and Weidle et al. (Gene, 98:185-191, 1991).

The claimed DNA construct comprising a coding sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence, and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site, is obvious in view of the disclosures of Meade et al. and DeBoer et al. as discussed in the above rejection.

The references of Meade et al. and DeBoer et al. do not disclose that the promoter can be selected from whey acid protein promoter or the lactalbumin promoter, that the immunoglobulin comprises heavy and light chains, or that the immunoglobulin is of human origin. However, Boss et al. disclose DNA sequences encoding immunoglobulin heavy and light chains which are capable of being expressed and assembled in transformed yeast cells (see, e.g., Figures 2 and 3, and column 22, line 1, through column 23, line 28). Bruggemann et al. Disclose the expression of a recombinant chimeric immunoglobulin in body fluids, including milk, of transgenic mammals (see, e.g., pages 11-13, under Example 2, Table 1, and Figure 5). Bruggemann et al. indicate that transgenic animals can be used for specific antibody production thus allowing large-scale production from milk, colostrums, sera, saliva, etc., as well as allowing the breeding of animals that yield a milk that is dosed with specific beneficial antibodies (see, e.g., page 12, last

paragraph, bridging page 13). In addition, Weidle et al. disclose a construct comprising DNA sequences encoding immunoglobulin heavy and light chains, which are capable of being expressed in transgenic mice, rabbits and pigs harboring the construct (see, e.g., Figures 1 and 2, and pages 186-187 under "Synthesis of reconstituted Ab in the serum of transgenic mice, rabbits and pigs"). From the teachings of Boss et al., Bruggemann et al., and Weidle et al. one of ordinary skill in the art would have had a high expectation of successfully producing a construct comprising a DNA sequence encoding a heterologous immunoglobulin sequence which can be expressed and assembled in a host cell or in the milk of a host mammal.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA construct of Meade et al. by providing a unique restriction site, such as XhoI between the promoter and 3' non-coding sequence as disclosed by DeBoer et al. for the purpose of providing a DNA construct which is amenable to accommodating the insertion of cDNAs encoding proteins of interest. It would also have been obvious to substitute different immunoglobulin cDNA sequences, such as those disclosed by Boss et al., Bruggemann et al., or Wiedle et al. as hosts transformed with plasmids containing DNA sequences encoding immunoglobulins are capable of synthesizing and secreting the immunoglobulins. Taken together, one of ordinary skill in the art would have had a high expectation of successfully producing a heterologous and assembled immunoglobulin in the milk of a transgenic mammal which harbors a DNA sequence comprising the coding region of an immunoglobulin operatively linked to a promoter which directs expression of a foreign protein in mammary tissue. As methods of modifying DNA constructs are well established in the molecular biology art for the purpose of obtaining constructs with desired properties, such as

tissue specific expression for secretion into milk, for example, and ease of insertion of various cDNAs of interest into the vector, one of ordinary skill in the art would have had a high expectation of successfully modifying the disclosed DNA constructs to obtain a DNA construct with tissue specificity, and a site for insertion of a desired cDNA without undue experimentation barring evidence to the contrary.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Applicant's arguments with respect to claims 19 and 22-30 have been considered but are moot in view of the new ground(s) of rejection.

Claims 19 and 22-30 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims1, 2, and 5 of U.S. Patent No. 5,750,172, May 12, 1998. Although the conflicting claims are not identical, they are not patentably distinct from each other because the expression system comprising a DNA sequence coding for a recombinant polypeptide chain operably linked to a casein promoter, wherein the recombinant

polypeptide chain is selected from immunoglobulins, and wherein the expression system is utilized in generating a transgenic mammal which secretes a recombinant protein into the milk of the mammal, as claimed in U.S. Patent No. 5,750,172, contains the same DNA sequence components claimed in the instant application. Moreover, the intended use of the claimed DNA construct of the instant application, i.e., for the expressing of the construct in mammary gland epithelial cells and secretes the immunoglobulin into the milk of the transgenic mammal, is encompassed in the patented claims. Although Meade et al. do not disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobin coding sequence is inserted into the restriction site, DeBoer et al. disclose a construct comprising the aS1 casein promoter and 3' non-coding sequence, and unique restriction sites, including XhoI, between the promoter and 3' non-coding sequence (see, e.g., Figures 5-7). Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the vector of Meade et al. by providing a unique restriction site, such as XhoI between the promoter and 3' non-coding sequence as disclosed by DeBoer et al. for the purpose of providing a vector which is amenable to accommodating the insertion of cDNAs encoding proteins of interest.

Sequence Compliance

As stated in the previous office action, this application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CRR. 1.821 (d) as reference must be made to the sequences disclosed on pages 10 and 11 in the text of the description by use of the sequence identifier, preceded by "SEQ ID NO:".

No claims are allowed.

All claims are drawn to the same invention claimed in the parent application prior to the filing of this Continued Prosecution Application under 37 CFR 1.53(d) and could have been finally rejected on the grounds and art of record in the next Office action. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing under 37 CFR 1.53(d). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0823. The examiner can normally be reached on 8:30-5:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J Clark can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian
August 10, 2001

REMY YUCEL, PH.D
PRIMARY EXAMINER